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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,564	11/30/2001	Andre Lieber	30429-2USWO	8863

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,564	LIEBER ET AL.	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *121-145* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *121-145* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11/27/02*. 5/29/02
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This office action is in response to an Amendment filed 12/5/03. Claims 59-120 have been cancelled. Claims 121-145 have been added. IDS' filed 11/27/02 and 5/29/02 have been identified and the documents considered. The signed and initialed PTO Form 1449s has been mailed with this action.

Election/Restrictions

Applicant's election with traverse of Group II (claims 63-64, 76-97 and 118-119) in the amendment filed 12/5/03 is acknowledged. The traversal is on the ground(s) that Group I does not lack inventive step over Wilson et al because Wilson et al does not teach the recombinant adenoviral vectors comprising the elements in the order as claimed. This is not found persuasive; the restriction requirement filed 10/2/03 pertaining to claims 59-120 does not apply to the newly submitted claims 121-145. Claims 121-145 are drawn to the same inventive group.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. Specifically, Denise Farrar has added #305 to the address. See 37 CFR 1.52(c).

Drawings

The drawings are objected to because Figure 17 contain parts, A and B and Figure 19 -20 contain parts C and D that are not described in the Brief Description of Figures. The Brief Description of Figures for Figure 18 describes Ad5/11 that does not appear in the figure. Figure 22 and 23 refer to Figure 8 text for further description of details; however, figure 8 does not correspond to the details indicated. In the Brief Description of Figures, Figure 29 refers to A-D, which are not found in the figure.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Specifically, there are sequences disclosed in figure 27 and claim 129 through claim 131 that do not have SEQ ID numbers associated with them. It would be remedial to include the appropriate SEQ ID NO's. If the sequences are not in the Sequence listing, a substitute sequence listing, CRF and statement that the two are the same and include no new matter should be submitted.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 131 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a New Matter rejection.

New claims 121-145 recite a recombinant adenovirus with left and right adenoviral ITRs, first and second adeno-associated ITRs and first and second inverted repeat sequences. Therefore, the limitation that there is a third set of repeat sequences in the adenoviral vector has been added to the claim. The invention teaches generation of an Adeno-AAV hybrid vector with a fiber protein that is designed to retarget the vector to desired cell types. The chimeric vector is comprised of Ad ITRs and AAV ITRs (see page 23, line 30 through page 24, line 2) but does not describe a third pair of inverted repeats. Support for the inclusion of inverted repeat sequences other than a single pair of adenovirus ITRs and AAV ITRS was not found in the specification and the applicant has not indicated where support exists for the inclusion of this limitation to the claims.

New Claim 131 recites peptide ligands comprised of amino acid sequences LNFCSFC and LNGCGXXXXXXXXXXGC. Support for the use of these sequences as ligands was not found in the specification. While applicant has indicated that support exists for the inclusion of these peptide sequences as ligands on page 14, line 27 and in Figure 27, these sections do not teach the use of these sequences.

Claims 121-145 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. ***.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) Nature of invention. The invention recites a recombinant double-stranded adenovirus vector where the "first strand" comprises three sets of ITR sequences such as from adenovirus and AAV as well as a heterologous promoter and a foreign gene sequence. The "second strand" encodes a modified adenoviral fiber protein, which alters the tropism of the adenovirus vector. The invention utilizes disciplines of molecular biology, cell biology and viral biology.

2) Scope of the invention. Combining the modification an adenoviral vector as described above creates a vector with altered or directed tropism for desired target cells and can integrate into the host chromosome. Each goal alone is complex and requires great skill in the art.

3) Number of working examples and guidance. The specification teaches how to generate adenoviral vectors that have AAV ITR sequences and foreign genes under the regulation of heterologous promoters inserted into an adenoviral vector. No guidance for sequences that are

meant to constitute the inverted repeats indicated in steps d and g is provided. Nor is a vector taught with three inverted repeats taught.

The adenoviral vectors are further modified by alteration or modification of the fiber proteins. The fiber proteins are truncated or deleted and replaced with fiber sequences (see page 83-86 which describes the generation of Ad5GFP/F35) from other serotypes or ligand peptide sequences are inserted into the fiber coding sequences (see page 95098 which describes insertion of ligands into GH loops). Neither of these examples teaches modification of the fiber encoding sequences such that **a second strand** encodes the modified fiber protein.

4) State of Art. The art teaches that the adenovirus genome is comprised of an r and l strand each encoding viral gene products. The fiber protein is encoded by the r-strand of the adenovirus genome. The r-strand also encodes the majority of functions as well as the regulatory functions of the ad ITR sequences (see e.g. Hitt, Advances in Pharmacology page 139).

5) Unpredictability of the art. The development of adenoviral vectors for gene therapy is a complex art that requires great skill in the art furthermore, modification of the integrative ability **and** the tropism of the vector simultaneously is very complex. The generation of a recombinant double-stranded adenovirus vector where the "first strand" comprises three sets of ITR sequences such as from adenovirus and AAV as well as a heterologous promoter and a foreign gene sequence and the "second strand" encodes a modified adenoviral fiber protein, which alters the tropism of the adenovirus vector is highly unpredictable given the lack of guidance in the instant specification. The specification does not teach what the source of all of the inverted repeats are to be nor does it teach how to modify the vector such that **the second**

strand encodes a modified fiber. It is not clear how the second strand can be modified to express a modified fiber protein.

6) Summary. The invention recites a complex series of methods for the generation of a modified vector with altered tropism and that integrates into the host chromosome. The unpredictability of making the claimed invention is accentuated due to the lack of processes disclosed in the instant specification exacerbate a highly unpredictable art.

In view of predictability of the art to which the invention pertains and the lack of established clinical protocols and the inability to predict for whom the therapies would be required: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 121-145 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 121-145 are vague and indefinite in that the metes and bounds of the "first strand" and the "second strand" are unclear. It is not clear whether the "first and second strands"

correspond to the r and l strands of the double-stranded adenovirus or to segments of DNA that are each double-stranded.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (703) 605-1207. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maria B Marvich, PhD
Examiner
Art Unit 1636

January 8, 2004

JAMES KETTER
PRIMARY EXAMINER